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Modeling Chemical Absorption Through Membranes

THESIS

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Modeling Chemical Absorption Through Membranes

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Jeffrey M. Hemmes

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Abstract

Understanding the processes involved in dermal penetration of chemicals and drugs is important to both toxicologists and pharmacologists. Researchers developing new drugs are interested in enhancing the penetration of chemicals through the skin, while environmental professionals are interested in limiting such penetration. For both types of applications, predictive biologically-based mathematical models can be very useful in understanding the processes involved, particularly when such models are based on physiological and biochemical parameters which can be measured experimentally. In this thesis we study two existing physiologically-based pharmacokinetic (PBPK) models that predict concentrations of neat and aqueous dibromomethane (DBM) absorbed into and through different types of membranes, namely rat skin and butyl rubber. We evaluate the models and add modifications as necessary to improve the predictions. Nearly all of the parameters in these two models are measured experimentally in a laboratory. Sensitivity analysis on the permeability coefficient, the only parameter that is estimated, shows how much of an effect that parameter has on the models' predictions. The objective in studying and developing these models is to gain a better understanding of the absorption process by first modeling simple membranes such as butyl rubber, and extrapolating the results for rat skin to other species such as humans.

Modeling Chemical Absorption Through Membranes

I. Introduction

1.1 Overview

In general, researchers do not know exactly what effect a chemical will have on the human body until actual experiments are performed. However, performing such experiments on humans is often infeasible because of the toxicity of many common chemicals. In order to understand a chemical's effects on the body without actually performing laboratory experiments, researchers have developed mathematical models to simulate the physical and chemical processes in the body. A physiologically-based pharmacokinetic (PBPK) model is a model that uses mathematical equations to represent the flow of a chemical through the body. The equations of a PBPK model contain physiological and biochemical parameters that are either measured experimentally or estimated. If the parameters can be measured in humans as well as laboratory animals, then experiments can be conducted on animals and possibly extrapolated to humans. This approach should increase understanding of the chemical effects while at the same time minimizing any risk to humans. Such extrapolation requires a thorough understanding of different types of skin structure. Modifications to the models, such as modeling additional skin subcompartments, may be necessary in order to account for differences between species. Performing sensitivity analysis on the parameters in the models can determine which have the greatest effect on the predictions and should be carefully measured in laboratory experiments.

1.2 Problem

Because the use of harmful chemicals is fairly commonplace in the Air Force, it is important to have a good understanding of the effects of such chemicals on humans.

Part of this understanding includes the ability to accurately predict the amounts and concentrations in various parts of the body after exposure. We have models that predict concentrations relatively well under certain conditions. However, the goal is to develop a general purpose mathematical model of dermal absorption that is based on biological parameters that are well understood and accurately measured experimentally. Such models can then be extrapolated across species to humans. Although there are several pathways through which chemicals can enter the body, e.g., ingestion and inhalation, the focus of this research is on dermal absorption.

1.3 Scope

This research evaluates two existing PBPK models, one based on an ordinary differential equation and the other based on a partial differential equation. Modifications to the partial differential equation model that improve the accuracy of the predictions are presented. Both models simulate percutaneous absorption of aqueous and neat, or concentrated, dibromomethane (DBM) liquid. These models determine the concentration of the chemicals in various parts of the body and do not account for any physical change in the skin caused by the chemical. Parameters for both models are measured experimentally. We determine the accuracy of both models by making comparisons between the models' output and experimental data collected from experiments involving rat skin and butyl rubber membranes. The results we obtained have not been extrapolated to any other species. However, the parameters are all biologically-based and may potentially allow for such extrapolation in the future. Furthermore, we performed a sensitivity analysis on the permeability coefficient, which in our research was considered to be a free parameter, in order to determine its effect on the models' predictions.

1.4 Approach

This research evaluated two existing models, an ordinary differential equation (ODE) model and a partial differential equation (PDE) model, and modified the boundary conditions of the PDE model to more accurately match experimental laboratory data. In this thesis, we

1. Reconstructed the ODE model previously published and verified the results using previously collected laboratory animal and butyl rubber data for DBM.
2. Reconstructed the PDE model and verified the results using previously collected animal data for DBM.
3. Modified the PDE model to improve the prediction for the mass passing through the membrane into the receptor cell.
4. Modified the boundary condition of the PDE model to improve the prediction for the mass into the skin for short term exposures.
5. Demonstrated that the variations of the ODE model which contain partition coefficients are equivalent if the permeability coefficients between donor and skin and between skin and receptor are not assumed to be identical.
6. Performed sensitivity analysis on both models and examined the impact of the free parameter in both models, the permeability coefficient, has on the computation.

1.5 Design Considerations

The two models presented and developed in this thesis should be able to predict blood concentrations of chemicals other than the ones discussed by using the appropriate biochemical parameters for a given chemical. For this research, we selected DBM for the validation of the models because it is one of the chemicals that the Operational Toxicology Branch of the Air Force Research Laboratory is currently interested in modeling [9]. The parameters for both of these models are all

biologically-based. Therefore, they should be measurable in humans, allowing the results to be extrapolated across species.

1.6 Summary of Thesis

The thesis is organized as follows:

Chapter II presents previous and current research being done in skin absorption and physiologically-based pharmacokinetic (PBPK) modeling. It also includes a discussion of laboratory experiments being done to support this research.

Chapter III presents the design and implementation of the models presented in chapter II.

Chapter IV presents the results of both the ordinary differential equation model and the partial differential equation model and compares these results to previously collected rat skin and butyl rubber data. It also includes sensitivity analysis which examines the impact that the free permeability parameter has on the results.

Chapter V presents both a summary of the work completed and the conclusions we reached. It also includes recommendations for future research in this area.

II. Background

2.1 Overview

Accurately predicting the amount of chemicals absorbed through dermal exposure requires a good understanding of the absorption process. McDougal [8] has investigated the effects of exposing membranes to organic solvents. These solvents were chosen specifically because of their hydrophobic and lipophilic, nature, meaning that they have no affinity for water, but are drawn to fats. This chemical property allows them to penetrate skin fairly well. Human skin and rat skin have numerous properties that affect the permeability of chemicals through the skin. Many of these properties are not completely understood. Before obtaining results for a complicated nonhomogeneous membrane such as rat skin, a thorough understanding of transport through a homogeneous membrane such as butyl rubber is needed. A number of studies have been done with the skin of rats and guinea pigs [4]. However, developing better models to predict the absorption through a simple membrane, particularly in non-steady state situations, must be done first.

The experiments that have been done involve a static diffusion cell. In these studies, a layer of rubber or skin is placed between a donor and a receptor cell. Typically, an aqueous dibromomethane (DBM) solution is placed in the donor cell, but other studies have involved pure liquid DBM. Inside the receptor cell is a saline solution. Concentrations in all three compartments are measured at different time intervals. This not only provides the amounts in each cell at different times, but also provides insight into other parameters, e.g. permeability, that determine the movement of chemicals through the membrane.

Simulating percutaneous absorption in humans using biologically-based mathematical models with parameters that are both measurable and meaningful is a long-term goal. However, because of the complexity of skin, simplified models have been developed which simulate absorption through a homogeneous membrane such

as butyl rubber. Once good reliable models can accurately predict the absorption of chemical through the rubber, they can be expanded to allow for the added complexity of skin. Furthermore, adding additional skin compartments to the models may be necessary to describe the absorption of substances that are not as lipophilic as DBM [1]. Two physiologically-based mathematical models have been developed to model this absorption.

2.2 Laboratory Experiments

Anatomical differences in skin structure are commonly thought to be responsible for varying rates of dermal absorption. Understanding how these differences affect such absorption can lead to the extrapolation of results for one species to others, including humans. In order to gain an understanding of how such differences affect absorption, it is necessary to design an experiment in which the differences in anatomical structure from other physiological factors such as metabolic rates, organ volume and blood flows. In addition, keeping the systems under study relatively simple makes mathematical modeling easier.

A desire for a relatively simple model were the reasons for studying absorption through butyl rubber. The rubber membrane, taken from butyl rubber gloves, has none of the additional structural complexities found in the rat skin. The objective was to gain a good understanding of absorption through a simple membrane. Once an model could be developed that accurately predicts the amounts absorbed into and through the simple rubber membrane, then the model could be adapted to a more structurally complex rat skin. Verifying the mathematical models required data sets for both types of membrane.

The experiments that have been done involve a static diffusion cell. In these studies, a layer of rubber or skin is placed between a donor and a receptor cell. Typically, an aqueous dibromomethane, or DBM, solution is placed in the donor cell, but other studies have involved pure liquid DBM. Inside the receptor cell is a

saline solution. Concentrations in all three compartments are measured at different time intervals [7]. This not only provides the amounts in each cell at different times, but also provides insight into other parameters, e.g. permeability, that would likely be used in a mathematical model.

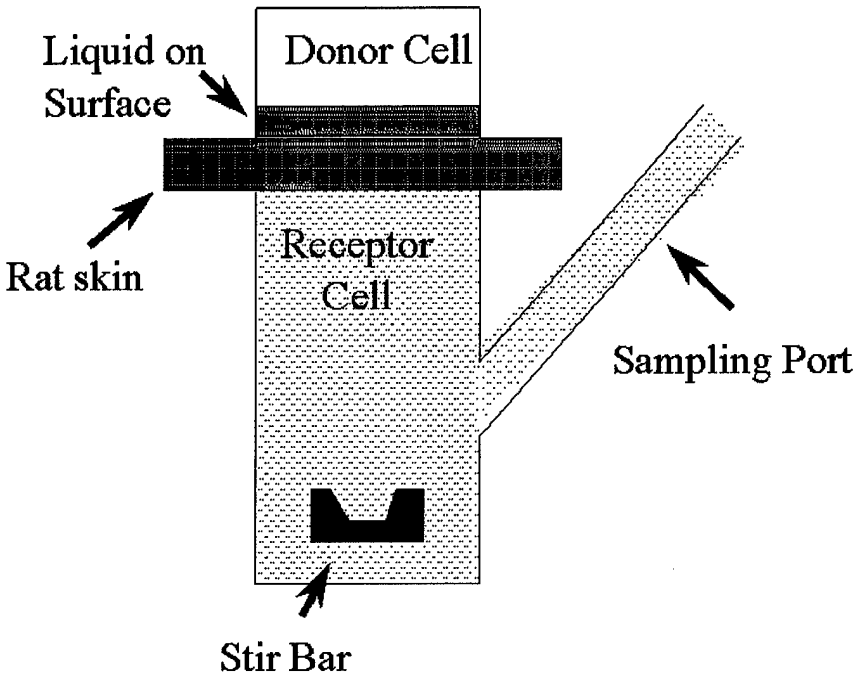

Figure 2.1 Static Diffusion Cell

2.3 Ordinary Differential Equation Model

2.3.1 Description. McDougal has developed an ordinary differential equation (ODE) model that has three compartments: a donor cell, the membrane, and a receptor cell. The transfer of mass in this model is dependent on a global permeability coefficient, which is the average of the permeability between the donor and rubber, and between the rubber and the receptor [6]. Each interface has its own permeability, and the relationship between the total permeability P and each individual interface permeability is given by [2]:

$$\frac{1}{P} = \frac{1}{P_1} + \frac{1}{P_2} \tag{2.1}$$

In general, if there are more than two interfaces, the reciprocal of the total permeability is equal to the sum of the reciprocals of all local permeabilities. In the ODE model, there are four interfaces where a permeability coefficient is used, two of which are directed inward. An experiment to determine the value of P for the interface between butyl rubber and the donor compartment has been performed [5]. We found that the permeability at this interface was very close to the average that had been used in previous models.

In this model the membrane compartment is assumed to be homogeneous, i.e., the skin consists only of a single well-stirred subcompartment. While this assumption is certainly appropriate for modeling absorption through butyl rubber, it may be possible to obtain better predictions by including additional subcompartments, as skin consists of several distinct layers that could be modeled separately. Bookout obtained accurate predictions by taking such an approach [1]. In any case, for the homogeneous skin model used here, the diffusion equations are derived from Fick's law [3]. The time rate of change of the mass of DBM in the donor cell, M_{don}, is described by:

$$\frac{d}{dt} M_{don} = PA \left(-\frac{C_{don}}{R_{don/sk}} + C_{sk} \right) \tag{2.2}$$

where

P = permeability coefficient between cell/membrane interfaces

A = surface area exposed to DBM

C_{don} = concentration of DBM in the donor compartment

C_{sk} = concentration of DBM in the membrane

$R_{sk/don}$ = partition coefficient between the donor and membrane

The time rate of change of the mass of DBM in the skin, M_{sk}, is described by:

$$\frac{d}{dt}M_{sk} = PA\left(\frac{C_{don}}{R_{don/sk}} - C_{sk}\right) + PA\left(\frac{C_{rec}}{R_{rec/sk}} - C_{sk}\right) \tag{2.3}$$

where

C_{rec} = concentration of DBM in the receptor compartment

$R_{sk/rec}$ = partition coefficient between the rubber and receptor

The time rate of change of the mass of DBM in the receptor, M_{rec}, is described by:

$$\frac{d}{dt}M_{rec} = PA\left(C_{sk} - \frac{C_{rec}}{R_{rec/sk}}\right) \tag{2.4}$$

The ODE model guarantees the conservation of mass in the system. The rate of change in the skin is the sum of the negatives of the rates from the donor and into the receptor cells. Initially, the concentrations in the skin and receptor are zero, so the mass is absorbed from the donor into the skin at a rate of $PAC_{don}/R_{don/sk}$ cm/hr. Since the initial rate of change from the donor cell is $-PAC_{don}/R_{don/sk}$ cm/hr, the rate in is equal to the rate out and thus mass is conserved.

In all models considered in this thesis the partition coefficient is used to adjust for the thermodynamic activity of the chemical in the receptor solution. The partition coefficient between medium A and medium B is defined as the concentration at equilibrium of the chemical in medium A divided by the concentration in medium B.

The ODE model is one of several developed in order to illustrate differences, the most simple of which contains only a donor and receptor cell with no partition coefficients. Other variations included partition coefficients and eventually a skin (or rubber) compartment. The ODE model used in this thesis contains both partition coefficients and a membrane compartment. Of this model, there are two variations, dubbed Four and Four-X. The membrane concentrations are weighted by the partition coefficients in model Four, and the concentrations in the donor and receptor compartment are weighted in model Four-X.

2.4 Partial Differential Equation Model

2.4.1 Description. A partial differential equation model of the same diffusion process has been developed that has differential equations describing the flux of only two compartments, rubber and receptor [11]. Because rubber is not infinitely well-stirred, the amount of chemical will vary at different points within it until equilibrium is reached. This model takes that variation in membrane concentration into account. From Fick's law, the equation describing the concentration of a chemical in the skin is

$$\frac{d}{dt}C_{sk} = D\frac{\partial^2 C_{sk}}{\partial x^2}. \tag{2.5}$$

Replacing the partial derivative with respect to x with a finite difference approximation yields

$$\frac{d}{dt}C_i = D\left[\frac{C_{i+1} - 2C_i + C_{i-1}}{\Delta x^2}\right] \tag{2.6}$$

where

D = the diffusivity of the chemical

$C_i(t) = C(x_i, t)$

The diffusivity for a particular chemical's absorption into a medium of a given thickness can be determined empirically by determining how long it takes the chemical to penetrate completely through that medium. By experimentally measuring L, the thickness of the membrane, and the lag time t_{lag}, the diffusivity can be calculated using the equation in Crank [3] or Bunge [10].

$$D = \frac{L^2}{6t_{lag}} \tag{2.7}$$

The rate of change of mass in the receptor cell is given by:

$$\frac{d}{dt}M_{rec} = PA\left(C_L - \frac{C_{rec}}{R_{don/sk}}\right) \tag{2.8}$$

where

M_{rec} = mass in the receptor

C_L = concentration of DBM in the membrane at the membrane/receptor interface

C_{rec} = concentration of DBM in the receptor

If M is the mass of the chemical and V is the volume, the amount of mass in the membrane is given by the equation

$$M_{sk} = \int_{\text{vol}} \frac{M}{V}\, dV \tag{2.9}$$

$$= \int_0^L CA \, dx \tag{2.10}$$

$$= A \int_0^L C \, dx \tag{2.11}$$

The integral is approximated numerically with a composite trapezoidal rule, so the amount in the rubber is simply the sum of all the interior rubber concentrations and the average of the concentrations at the interfaces, multiplied by the area A and Δx, i.e.,

$$M_{sk} = A\Delta x \left[\sum_{i=1}^{N-1} C_i + \frac{1}{2}(C_0 + C_N) \right] \tag{2.12}$$

where N is the number of compartments in the skin, L is the thickness, and $\Delta x = L/N$. The equation for the total mass absorbed is derived from Fick's first law, given as:

$$\Delta M_{in} = -DA \frac{\partial C}{\partial x} \Delta t \tag{2.13}$$

In this model, a finite difference approximation is used to compute the partial derivative of the concentration. As in the ODE model, the parameters for this model were measured experimentally in the laboratory.

Validation of the PDE model requires that it not only matches the laboratory data, but that it conserves mass over time as well, i.e., the total mass absorbed should equal the sum of the mass in the skin and the mass in the receptor cell. Earlier calculations using the PDE model showed that there was a small increase in the mass absorbed over time, although the mass gained at each time step Δt was very small. Furthermore, we also determined empirically that although the system did reach steady state in the skin, and the results there were reasonably accurate

for butyl rubber, the amount in the receptor did not reach equilibrium and the predictions did not match the experimental data.

2.4.2 Boundary Conditions. Initially, there is no chemical in the skin, except at the interface at the donor cell. The initial surface concentration is the concentration in the donor cell multiplied by the partition coefficient for the donor and the rubber. The equation is given by:

$$C_0 = \frac{M_{dose}}{V_{don}} R_{sk/don} \tag{2.14}$$

where M_{dose} is the amount of the chemical initially in the donor cell.

Equation 2.14 is based on an assumption made in an earlier paper by Cleek and Bunge that a constant concentration in a vehicle substance will reach equilibrium with the outermost layer of the stratum corneum in the skin instantaneously [10]. Since the initial concentrations on both sides of the interface between the skin and the receptor are zero, local equilibrium is still established, although the concentration is zero. At the interface between the donor and the skin, the concentration is nonzero as there is an initial donor concentration of M_{dose}/V_{don}. Making such an assumption in this model resulted in an overprediction in the skin for relatively short term exposures, i.e. less than one hour. Figure 2.2 shows the prediction of the model compared to experimental rat skin data exposed for twenty-four minutes. The parameter values are the same as those displayed in Table 3.1 later in this thesis.

The rate of change of the amount in the skin depends on whether the DBM is aqueous, i.e., dissolved in water, or neat, i.e., pure. For aqueous donor solution, the concentration in the donor decreases as the chemical is absorbed into the skin. For neat DBM, the concentration remains constant, and so the derivative with respect to time is zero. For aqueous DBM, the amount in the donor is:

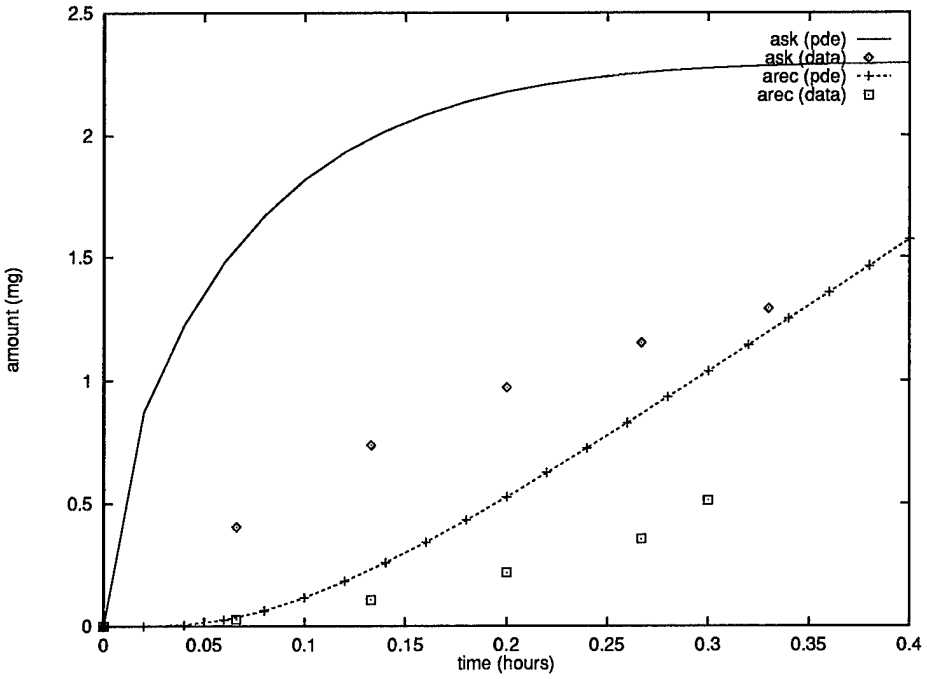

Figure 2.2 Rat Skin PDE Model Results. In this case the original PDE model's predictions are very high for the amounts in both the skin and the receptor.

$$M_{don} = M_{dose} - M_{in} \tag{2.15}$$

2.5 Summary

This review has presented two physiologically-based mathematical models for predicting chemical absorption. One model is a system of ordinary differential equations; the other, a partial differential equation coupled with two ordinary differential equations. Reviewing the previous work has revealed the basic approaches used in developing pharmacokinetic models. The background discussed in this chapter is the foundation for evaluating and further developing the models.

III. Model Design and Implementation

3.1 Overview

A number of physiologically-based pharmacokinetic models have been developed to predict the effect of chemicals in a mammal after dermal absorption. The models are based on biological and physiological parameters that can be measured. The results using one species, i.e., a rat, can be extrapolated to other species, including humans. A model that can accurately predict absorption through rat skin has the potential to be modified and then used to predict the effect in humans.

We have taken previously developed models and evaluated their ability to predict dermal absorption using parameters measured in a laboratory. We have modified them somewhat to obtain better agreement with the laboratory results. The main focus is not simple curve fitting; it is to develop the best possible model that minimized the number of uncertain parameters yet still made sense from a physiological standpoint.

3.2 Computational Methods

The existing models had previously been implemented using Fortran 77 and a commercial subroutine called IVPAG, from the International Mathematics and Statistics Library (IMSL) [11]. IVPAG was designed to solve an initial value problem for ordinary differential equations using an Adams-Moulton or Gear Method. One of our goals was to take advantage of the computational power of desktop computers and move away from the workstations on which previous models had run. In order to do this, we selected the Livermore Solver for Ordinary Differential Equations (LSODE) subroutines. Like IVPAG, the LSODE subroutine is based on the Gear method for stiff systems. However, unlike IVPAG, the source code for LSODE was available, which provided the opportunity to port programs to other environments. In addition, models have also been written in ACSL, a programming language used

by the Toxicology Branch of the Air Force Research Laboratory for their dermal absorption models. Using the results from the ACSL programs allows us to triple check the models for consistency.

3.3 Initial Attempts

Before using the LSODE library to solve the problems of chapter two, we took a simple ordinary differential equation for which the analytic solution is known and wrote a program to calculate the numerical solution at a number of points. The equation is:

$$y'' = -y \tag{3.1}$$

with initial conditions

$$y(0) = 1$$

$$y'(0) = 0$$

and analytic solution $y = \cos t$.

The LSODE routines were written in Fortran 77. Because of personal preference, we wanted to use them in programs written in the C programming language. In order to determine how to link the object code that was provided we used a Fortran to C translator to convert the source code to C, then compiled the files with the gcc compiler. Once we did the translation, recompilation, and linking, we had an executable program. We ran the program and compared the results to the analytic solution to the differential equation. The results from the program were almost accurate to machine precision, so at that point we decided to use the LSODE subroutine for our work.

3.4 Ordinary Differential Equation Model Implementation

Once we had a correct program that successfully called the LSODE routines, we were ready to begin porting the models described in chapter two to the PC. One of the reasons for switching from IVPAG to LSODE was to be able to run the models on PC platforms running either MSDOS or Linux. Using both an ACSL code and a Fortran implementation of the ODE model as a guide, we wrote a new implementation of the models of [6] and [11] in C. Once a few syntactical details were worked out, the results of our program were identical to both the ACSL and the Fortran results.

For the parameters, we used values measured experimentally. Our objective in creating the model was primarily to recreate the results obtained earlier using ACSL. At this point we were not attempting to modify the ODE model in any way. The parameter values used in the original program were also used in the new program, and the predicted values were identical. As much as possible, the experimentally measured parameters were used in the models. Table 3.1 lists all constants used for rat skin, while Table 3.2 lists constants used for neat DBM with butyl rubber, and Table 3.3 lists constants used with aqueous DBM with butyl rubber.

The following relationships are used to compute the constants found in equations 2.2, 2.3, and 2.4:

$C_{don} = A_{don}/V_{don}$

$C_{sk} = A_{sk}/V_{sk}$

$C_{rec} = A_{rec}/V_{rec}$

$V_{sk} = AL$

$R_{don/sk} = R_{don}/R_{sk}$

$R_{rec/sk} = R_{rec}/R_{sk}$

3.4.1 Partition Coefficients in the ODE Model. Earlier in chapter II it was mentioned that regardless of how the concentrations were weighted with the partition

Constants	Values
L (cm)	0.1105
M_{dose} (mg)	113.7
V_{don} (cm^3)	10.0
V_{sk} (cm^3)	0.54145
V_{rec} (cm^3)	12.94
R_{don}	14.40
R_{sk}	8.33
R_{rec}	20.0
A (cm^2)	4.9
P (cm^3/sec)	0.22
$M_{don,avg}$ (mg)	112.526
$M_{sk,avg}$ (mg)	0.8354
$M_{rec,avg}$ (mg)	0.2482

Table 3.1 Parameter Values for Aqueous DBM Through Rat Skin

Constants	Values
L (cm)	0.05
M_{dose} (mg)	4994.0
V_{don} (cm^3)	2.0
V_{sk} (cm^3)	0.245
V_{rec} (cm^3)	14.11
R_{don}	6211.0
R_{sk}	81.2
R_{rec}	9.0
A (cm^2)	4.9
P (cm^3/sec)	0.0151
$M_{don,avg}$ (mg)	4818.92
$M_{sk,avg}$ (mg)	120.155
$M_{rec,avg}$ (mg)	143.986

Table 3.2 Parameter Values for Neat DBM Through Butyl Rubber

Constants	Values
L (cm)	0.05
M_{dose} (mg)	113.0
V_{don} (cm^3)	11.06
V_{sk} (cm^3)	0.245
V_{rec} (cm^3)	12.94
R_{don}	14.40
R_{sk}	81.2
R_{rec}	20.0
A (cm^2)	4.9
$M_{don,avg}$ (mg)	59.3091
$M_{sk,avg}$ (mg)	4.4419
$M_{rec,avg}$ (mg)	39.8883

Table 3.3 Parameter Values for Aqueous DBM Through Butyl Rubber

coefficients, the ODE model gives the same results if the permeability coefficients are allowed to be different, local permeabilities. This is easy to show algebraically. Start with equation 2.2 of the ODE model used in this thesis (the model McDougal has labeled four-x) [6]:

$$\frac{d}{dt}M_{don} = P_1 A \left(C_{sk} - \frac{C_{don}}{R_{don/sk}} \right) \tag{3.2}$$

then factor out $\frac{1}{R_{don/sk}}$, or $R_{sk/don}$.

$$\frac{d}{dt}M_{don} = R_{sk/don} P_1 A \left(\frac{C_{sk}}{R_{sk/don}} - C_{don} \right) \tag{3.3}$$

This can be done similarly for the mass equation for the receptor cell,

$$\frac{d}{dt}M_{rec} = P_2 A \left(C_{sk} - \frac{C_{rec}}{R_{rec/sk}} \right) \tag{3.4}$$

producing the equation

$$\frac{d}{dt}M_{rec} = R_{sk/rec}P_2A\left(\frac{C_{sk}}{R_{sk/rec}} - C_{rec}\right) \tag{3.5}$$

If equation 2.3 contains two permeabilities, P_1 and P_2, it becomes

$$\frac{d}{dt}M_{sk} = P_1A\left(\frac{C_{don}}{R_{don/sk}} - C_{sk}\right) + P_2A\left(\frac{C_{rec}}{R_{rec/sk}} - C_{sk}\right) \tag{3.6}$$

Now if we factor out $R_{don/sk}$ and $R_{rec/sk}$ from the terms in 3.6 and allow $P_1{}' = R_{sk/don}P_1$ and $P_2' = R_{sk/rec}P_2$, the equation for the rate of change of the mass in the skin is

$$\frac{d}{dt}M_{sk} = P_1'A\left(C_{don} - \frac{C_{sk}}{R_{sk/don}}\right) + P_2'A\left(C_{rec} - \frac{C_{sk}}{R_{sk/rec}}\right) \tag{3.7}$$

Consistent with equation 3.7, we replace $P_1R_{sk/don}$ with P_1' in equation 3.3 and replace $P_2R_{sk/rec}$ with P_2' in equation 3.5. Figure 3.1 shows that the derived equations are equivalent to the original equations computationally as long as the permeability coefficient P_1 is not necessarily equal to P_2.

Model 4x uses equations 2.2, 2.3, and 2.4 with parameters from table 3.1. Model 4 uses equations 3.3, 3.4, and 3.7 with the parameters from table 3.1 with $P_1' = R_{sk/don}P_1$, and $P_2' = R_{sk/rec}P_2$.

3.5 Partial Differential Equation Model Implementation

The PDE model poses several challenges compared to the ODE model because it requires the solution of a system of ordinary differential equations to obtain M_{sk}, and not the single equation as in the ODE model. Solving a system of equations rather than a single equation added to the complexity of the implementation.

Like those of the ODE model, the values of the parameters in the PDE model were taken from laboratory experiments. The only variable that we consider to be free is the permeability coefficient. The value of P was taken from earlier ACSL

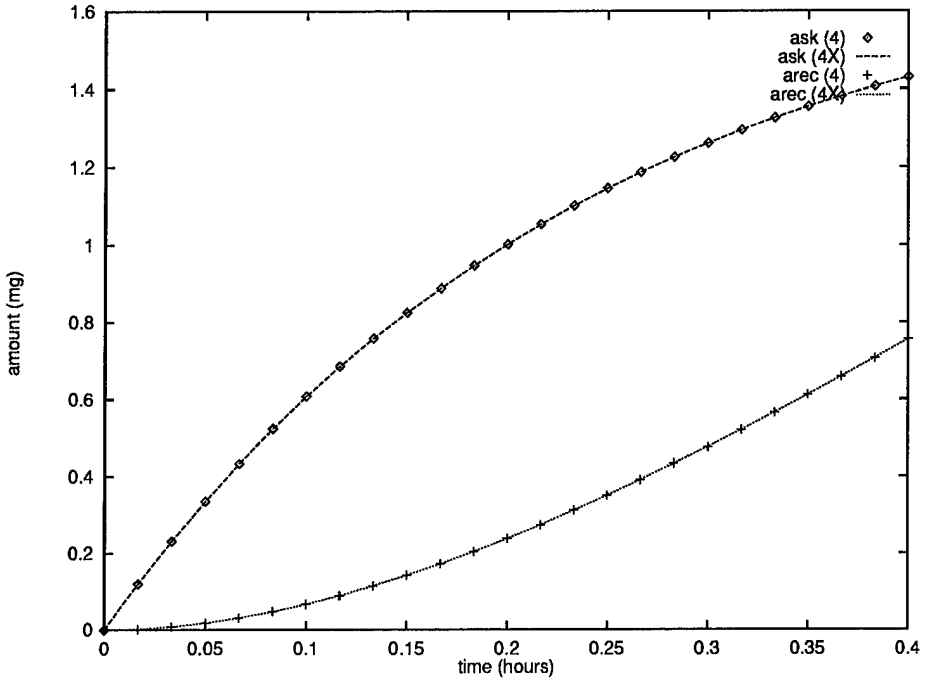

Figure 3.1 This graph shows that variations of the ODE model with different weights on the concentrations are equivalent.

implementations of the ODE model. Using a value of $P \approx 0.22$ generally produced results that were reasonably close to the experimental data for aqueous DBM. The value differs from that used in the ODE model, but other parameters' values were the same. The lag time, t_{lag} is not included in the ODE model, but its value was determined graphically from a plot of laboratory data.

3.6 Changes to the Partial Differential Equation Model

The initial version of the PDE model did not produce satisfactory results for aqueous DBM. The model overpredicted the amount in the skin compartment for times less than about one hour, as indicated by figure 2.2. At equilibrium the amount predicted closely matched both the experimental data and the prediction of the ODE model. The error appeared to be due to a miscalculation of the concentration in the donor cell. With neat DBM, the concentration does not change with time, but

with aqueous DBM, the concentration in the donor compartment decreases until equilibrium is reached. Including this concentration change in the model improved the results, but the amount in the skin was still in error.

The solution to this problem involved explicitly modeling the change in mass in the donor compartment. The equation for the amount in the donor cell is given by:

$$M_{don} = M_{dose} - M_{in} \tag{3.8}$$

where M_{in}, the total mass absorbed, is obtained by integrating equation 2.13. We want to have an equation for the mass in the donor which is similar to that for the receptor given by equation 2.4, i.e.,

$$\frac{d}{dt}M_{don} = P_{don}A\left[\frac{C_1}{R_{sk/don}} - C_{don}\right] \tag{3.9}$$

where $C_{don} = M_{don}/V_{don}$, and C_1 is the concentration in the skin at the skin/donor interface. The equation describing the mass in the receptor is

$$\frac{d}{dt}M_{rec} = P_{rec}A\left[\frac{C_L}{R_{sk/rec}} - C_{rec}\right] \tag{3.10}$$

where C_L is the concentration in the skin at the skin/receptor interface.

To derive the new boundary condition for the PDE model, we recall from 2.13 that the total mass absorbed is given by

$$\frac{d}{dt}M_{in} = -DA\frac{\partial C}{\partial x} \tag{3.11}$$

Differentiating both sides of equation 3.8 gives

$$\frac{d}{dt}M_{don} = -\frac{d}{dt}M_{in} \tag{3.12}$$

Substituting equation 3.11 for $\frac{d}{dt}M_{in}$ in equation 3.12 above, we have

$$\frac{d}{dt}M_{don} = DA\frac{\partial C}{\partial x} \tag{3.13}$$

Equating the right hand side of equation 3.9 to the right hand side of equation 3.13 yields

$$DA\frac{\partial C}{\partial x} = P_{don}A\left[\frac{C_1}{R_{sk/don}} - C_{don}\right] \tag{3.14}$$

or

$$\frac{\partial C}{\partial x} = \frac{P_{don}}{D}\left[\frac{C_1}{R_{sk/don}} - C_{don}\right] \tag{3.15}$$

Using a finite difference approximation for the left hand side of equation 3.15 above, we have

$$\frac{C_2 - C_1}{\Delta x} = \frac{P_{don}}{DR_{sk/don}}C_1 - \frac{P_{don}}{D}C_{don} \tag{3.16}$$

Multiplying both sides of equation 3.16 by Δx gives

$$C_2 - C_1 = \frac{P_{don}\Delta x}{DR_{sk/don}}C_1 - \frac{P_{don}\Delta x}{D}C_{don} \tag{3.17}$$

Grouping all C_1 terms on the left hand side with all other terms on the right hand side yields

$$\left[1 + \frac{P_{don}\Delta x}{DR_{sk/don}}\right]C_1 = C_2 + \frac{P_{don}\Delta x}{D}C_{don} \tag{3.18}$$

Finally, differentating both sides of equation 3.18 with respect to t gives

$$\frac{d}{dt}C_1 = \left[\frac{d}{dt}C_2 + \frac{P_{don}\Delta x}{DV_{don}}\frac{d}{dt}C_{don}\right]\left[1 + \frac{P_{don}\Delta x}{DR_{sk/don}}\right]^{-1} \tag{3.19}$$

Including this equation causes the amount in the skin to increase less rapidly than before, because we no longer assume that the surface reaches equilibrium instantaneously. However, at equilibrium the amount in the skin still matches the experimental data as before.

Although this change in the boundary condition improves the predictions in all three compartments, there is one difficulty: The IVPAG routine can solve the equations with little difficulty, but we were unable to successfully run the program using LSODE. Numerous attempts were made to solve the amount in the donor cell analytically with an algebraic equation, but in all cases the maximum number of iterations allowed by LSODE (which we also manually increased) was exceeded. This is a topic that would be appropriate for further study.

3.7 Summary

We have taken the ODE model developed by McDougal [6] and the PDE model developed by Quinn [11] and implemented them using the LSODE software library so that we could compare the results of both models against each other as well as experimental laboratory data. Our objective has been and continues to be to find the model that most accurately predicts the amounts in all compartments for both rubber and rat skin for both short-term and long-term experiments. In addition, the parameters for these models are measured in a laboratory, and thus are more biologically meaningful. We have extended the PDE model to more accurately model the absorption at the interface between the skin (or rubber) and the donor compartment. Both models predict the amounts in the three compartments with a reasonable degree of accuracy, but the PDE model provides more accurate predictions in several cases.

IV. Model Results

4.1 Overview

In this chapter the predictions of both the ordinary differential equation (ODE) and the partial differential equation (PDE) models are compared to experimental data. Data exist for aqueous dibromomethane (DBM) through both rat skin and butyl rubber, and for neat DBM through rubber. The models simulate the time periods over which the membranes were exposed in the experiments. The sum of squared deviations and graphical plots are used to determine not only how well the models predict the amounts measured empirically in each cell over time, but also to determine the optimal permeability coefficient for each membrane. Sensitivity analysis performed on the skin or rubber compartment parameters demonstrate how much of an effect the permeability coefficient has on the predicted concentrations in the membrane and in the receptor.

4.2 Ordinary Differential Equation Model Predictions

The receptor cell predictions from the ODE model are compared to data collected from five different laboratory experiments. In one experiment, rat skin was exposed to aqueous DBM for twenty-four minutes. In another, butyl rubber was exposed to neat DBM for three hours. In two others, butyl rubber was exposed to aqueous DBM for three hours and 120 hours respectively. In the fifth experiment, a three-hour experiment, the diffusion cell did not contain a receptor. The purpose of having no receptor was to obtain a more accurate measurement of the parameters in modeling donor to membrane absorption.

4.2.1 Aqueous DBM Through Rat Skin. The parameters for the rat skin model are given in Table 3.1. Figure 4.1 shows how the ODE model compares to the experimental data for the skin and receptor cells. Figure 4.2 shows the results

for the donor cell. In the experiment, rat skin was exposed to 113.7 milligrams of aqueous DBM (with initial concentration 11.37 mg/mL) for a period of twenty-four minutes. The ODE model predicted the amounts in both the skin and in the receptor extremely well in this case. The sum of squared deviations between the model prediction and the data is 0.000301 for the skin, 0.0029 for the receptor, and 5.022×10^{-8} for the donor compartment. The sum of squared deviations is calculated using the formula

$$S = \sum_{i=1}^{N} [(P_i - O_i)/W_T]^2$$

where O_i is the observed value at point i, P_i is the model prediction for O_i, and W_T is the average value listed as M_{don},M_{sk}, or M_{rec} in Tables 3.1, 3.2, and 3.3, respectively.

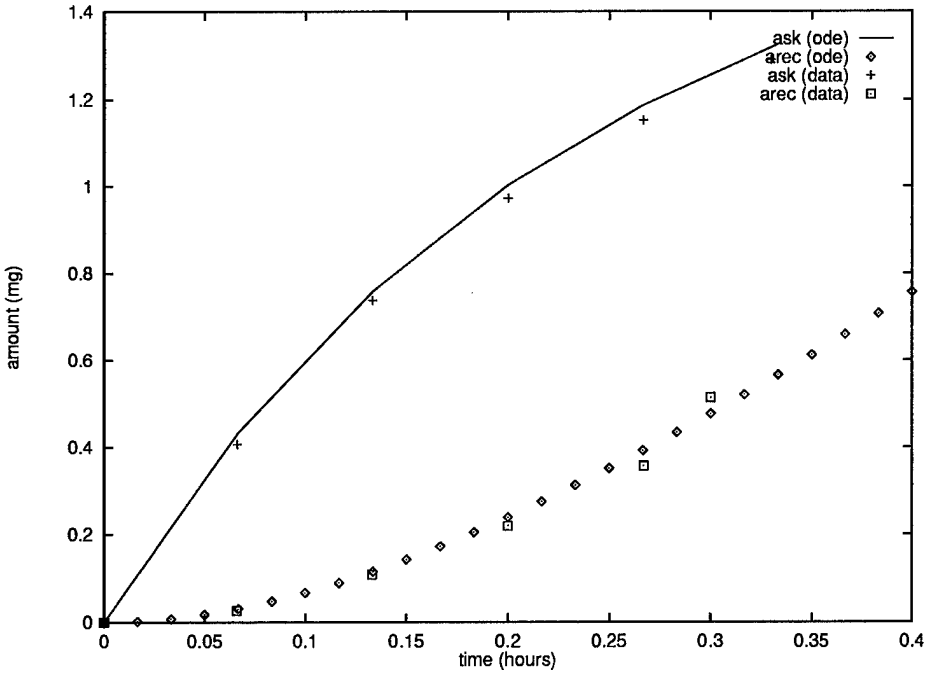

Figure 4.1 Aqueous DBM Rat Skin ODE Model Results. The graph shows that the ODE model very accurately predicts the amount in both the skin and receptor compartments. A permeability coefficient of $P = 0.22$ was used in this case.

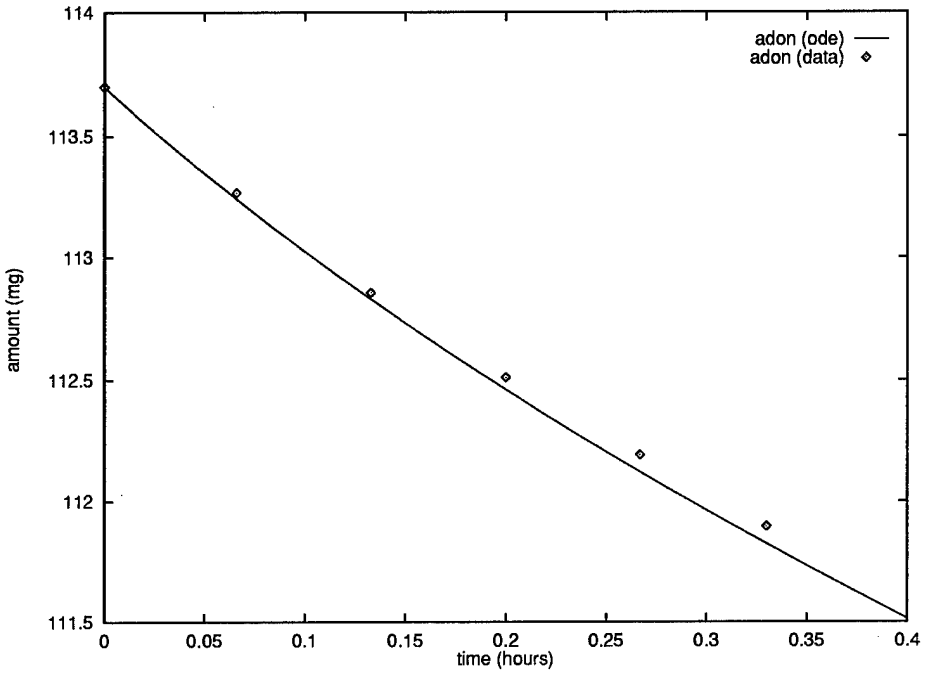

Figure 4.2 Aqueous DBM Rat Skin ODE Model Results. The graph shows that the ODE model very accurately predicts the amount in the donor compartment.

4.2.2 Neat DBM Through Butyl Rubber. The ODE model does not accurately predict the amount in any compartment for neat DBM. We ran numerous trials, each time varying the parameters, but were unable to match the laboratory data. This suggests that a different model may have to be designed for neat DBM or other concentrated chemicals. Determining exactly how to compute the initial dose of neat DBM is also a subject for future study. Current estimates are calculated using the molecular weight of the chemical, but this method may not be appropriate.

By adjusting the permeability and the initial dose, the model can fairly accurately predict the amount of chemical that passes through into the receptor. However, the amount in the skin reaches equilibrium rapidly and does not reach the levels measured experimentally. Using vastly different permeabilites for absorption into and out of the rubber did not significantly affect the results. Figure 4.3 shows the results of the model for the receptor cell. Similar results were obtained for the amounts in the skin compartment, while the amount in the donor cell was high in comparison to the experimental data. Regardless of the permeability, the ODE model always reaches equilibrium far earlier than the experimental data indicates.

4.2.3 Aqueous DBM Through Butyl Rubber Without Receptor. The ODE model does not accurately predict the amount in the skin or in the donor in this case. Figures 4.4 and 4.5 show that although overall the shape of the curves are about right, the total amount absorbed is very low compared to the laboratory data. The sum of squared deviations for the amount in the skin is 1.2274, and for the donor is 0.0632. Changing the permeability coefficient does not have a significant effect on the results. Table 4.2 shows that a five percent increase in the permeability increases the sum of squared deviations by 1.16 percent.

Similar results were obtained with both models Four and Four-X. In both cases, equilibrium is reached before the predicted amount in the rubber matches the experimental data.

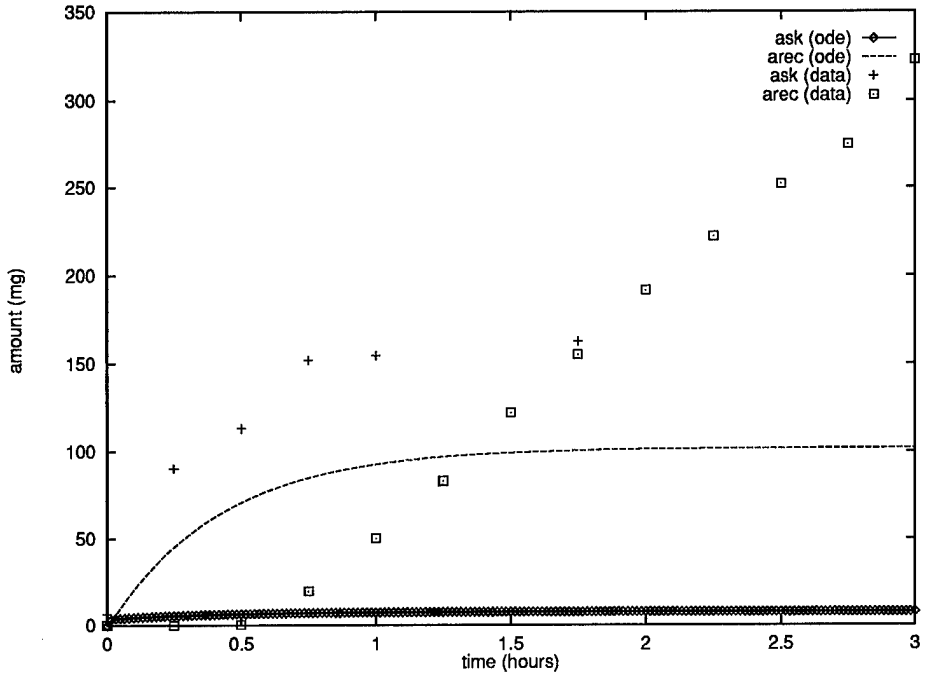

Figure 4.3 Neat DBM Through Butyl Rubber Results. The graph shows that the ODE model does not accurately predict the amount in the membrane or receptor cell.

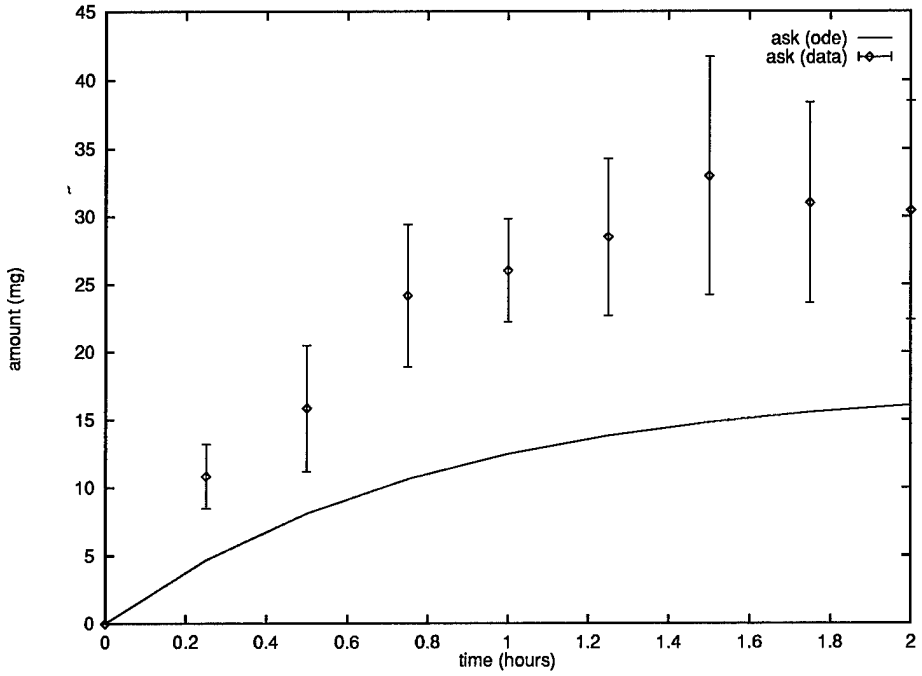

Figure 4.4 Aqueous DBM Butyl Rubber ODE Model Results With No Receptor. The graph shows that the ODE model underpredicts the amount in the skin in this case. Error bars indicate the range of results for multiple experiments. A permeability coefficient of $P = 0.22$ was used.

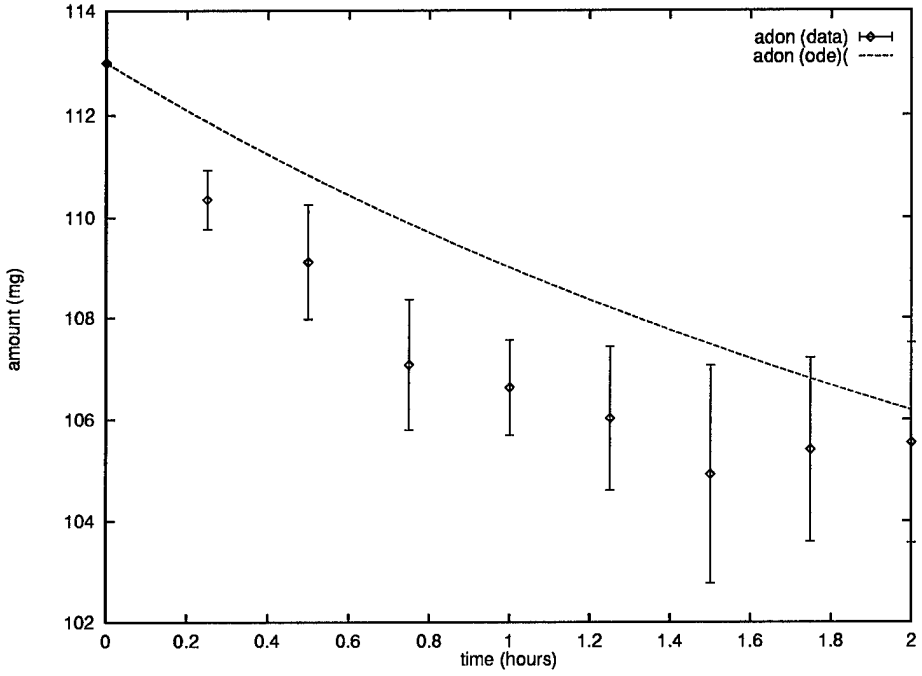

Figure 4.5 Aqueous DBM Butyl Rubber ODE Model Results With No Receptor. The graph shows that the ODE model overpredicts the amount in the donor in this case. Error bars indicate the range of results for multiple experiments.

4.2.4 Aqueous DBM Through Butyl Rubber With Receptor. Laboratory experiments were conducted on butyl rubber for both intermediate and long term exposures to aqueous DBM. Figure 4.6 shows the predictions for the amounts in both the rubber and the receptor over five days, and figure 4.7 shows the prediction for the amount in the donor. Generally speaking, the ODE model does a good job of predicting the amounts in all three compartments over both time intervals. However, the amount that passes through the rubber and into the receptor is a bit high, and therefore the model also underpredicts the amount in the donor cell. The sum of squared deviations for the amount in the skin is 0.3922, for the donor is 0.0676, and for the receptor is 0.1274.

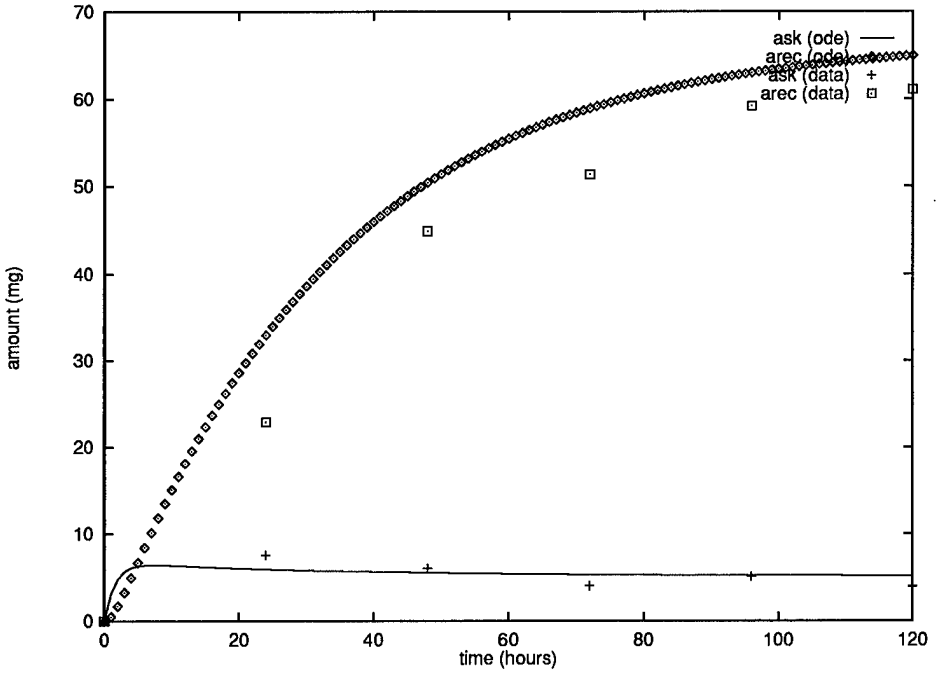

Figure 4.6 Aqueous DBM Butyl Rubber ODE Model Results With Receptor Cell. The amounts predicted by the ODE model are fairly accurate for both the rubber and the receptor cell. A permeability coefficient of $P = 0.0151$ was used in this case.

4.2.5 Sensitivity Analysis for the ODE Model. Nearly all parameters used in both models were measured in the laboratory, and are considered fairly accu-

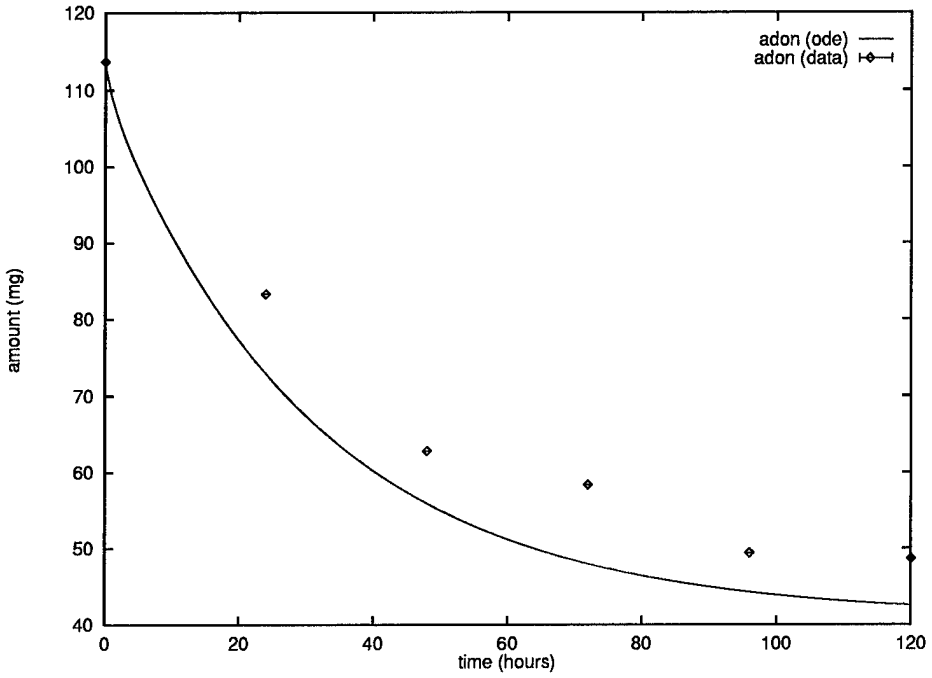

Figure 4.7 Aqueous DBM Butyl Rubber ODE Model Results With Receptor Cell. The amounts predicted by the ODE model are accurate for the donor cell.

rate [4]. In the case of the ODE model, the permeability coefficient, which is actually an average of the permeabilty between both surfaces of the rubber, is the only parameter not measured experimentally. Ordinarily, the permeability can be determined from the slope of the graph. However, in experiments such as this in which the concentration changes, that is not possible, so there is some freedom to optimize. Because if this uncertainty, we performed a sensitivity analysis on this parameter to see to what extent its value affected the predictions of the model.

The methodology for the performing the sensitivity analysis was quite simple. We adjusted the permeability coefficient five percent, then calculated the new sum of squared deviations. The permeability coefficient was selected as the parameter for this analysis because the methods by which the other parameters are measured are well-defined and there is a good deal of confidence in the values used in the model [6]. Furthermore, Bookout showed that in similar pharmacokinetic models, the blood concentrations were most sensitive to the permeability [1]. After changing the permeability coefficient and running the models, we found that in the ODE model, the effect on the values for each compartment is substantial. Table 4.2 shows the sum of squared deviations for both models after the permeability coefficient is increased five percent along with the percent change in the total sum of squares.

4.3 Partial Differential Equation Model Predictions

In this section, the results of the PDE model are compared to both the laboratory data described in the preceding section as well as to the results of the ODE model. Our goal is to determine which of the two models more accurately predicted the amounts in all three compartments. Because both models predict the same pharmacokinetic process, those predictions should be fairly similar. However, because of the PDE model takes into account the heterogeneous nature of the skin or rubber, there should be differences between the two models' results.

4.3.1 Aqueous DBM Through Rat Skin. Using equation 3.8 to calculate the amount in the donor compartment yielded inaccurate predictions for the amount in the skin. Using the boundary condition of equation 3.8, the model substantially overpredicts the skin concentration for short time intervals. Figure 2.2 shows the extent to which the PDE model overpredicts. The sum of squared deviations for the original PDE model is 10.7914 for the skin, 21.8568 for the receptor, and 0.0011 for the donor cell. Figure 4.8 shows that the use of equation 3.9 to calculate the amount in the donor cell results in a much closer match between the model predictions and the empirical data. In this case the weighted sum of squared deviations is 0.2177 compared to the data for the skin, 9.3244×10^{-6} for the donor, and 0.1452 for the receptor, a substantial improvement over those of the original PDE model, listed in Table 4.1.

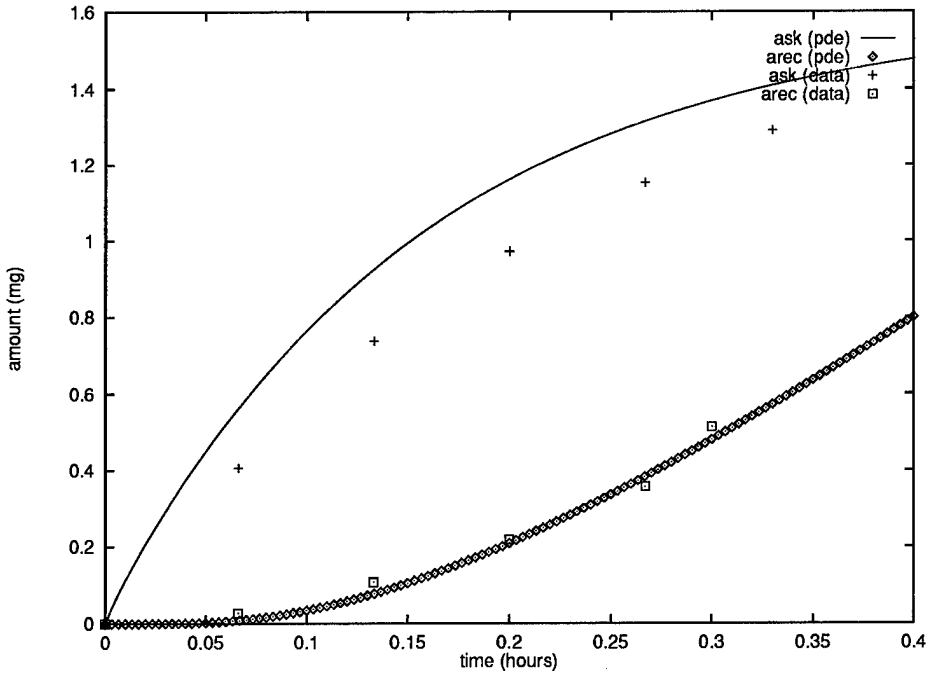

Figure 4.8 Aqueous DBM Rat Skin PDE Model Results. In this case the PDE model's predictions are slightly high for the amount in the skin, but the amount in the receptor is very close.

The earlier PDE model also does not conserve mass. The increase at each time interval is slight, but there is a steady increase in the total mass in the system until equilibrium is reached. The modification to the PDE model does not eliminate this mass gain entirely, but it does reduce it considerably. Figure 4.9 shows the comparison between the total mass in the original PDE model versus that in the modified model.

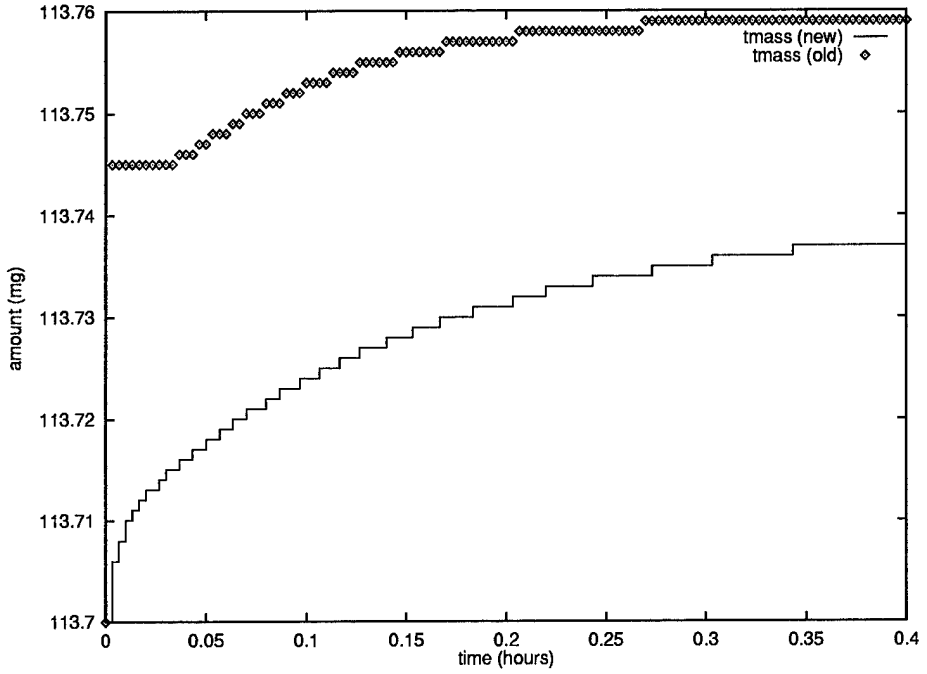

Figure 4.9 Total Mass Absorbed in the PDE Model. This graph shows that the new boundary condition in the PDE model improves the conservation of mass. These results are for the 24-minute exposure of aqueous DBM to rat skin

4.3.2 Neat DBM Through Butyl Rubber. The same questions concerning the parameter values that affected the ODE model's predictions for neat DBM also apply to the PDE model. Again, repeated trials were attempted, each time varying the initial dose and concentration in the donor cell, but we were not able to produce any satisfactory results. In addition, changing the permeability does not have any significant effect on the results. Figure 4.10 shows the model's predictions for the

amount in the receptor compartment. The predicted amount in the receptor is so small it lies on the t-axis. Similar results were obtained for the skin compartment, while the amount in the donor cell was high in comparison to the experimental data.

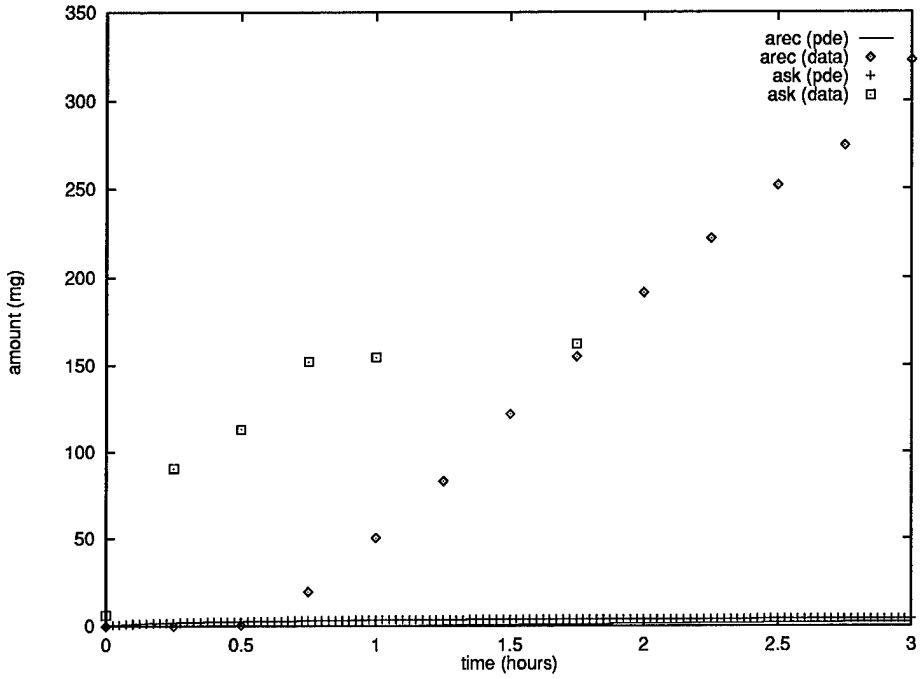

Figure 4.10 Neat DBM Through Butyl Rubber Results. The graph shows that the PDE model does not accurately predict the amount in the receptor cell.

4.3.3 Aqueous DBM Through Butyl Rubber Without Receptor. The PDE Model accurately predicts the amount of chemical absorbed into the rubber when there is no receptor compartment. However, the model appears to overpredict the amount in the donor. Since the amount in the rubber is at equilibrium, we assume that the amount in the donor cell must also reach equilibrium at the same time. Therefore, the apparent overprediction by the model can be attributed to evaporation of the DBM in the laboratory experiment or other experimental error.

The amount in the skin in the PDE model is a function of, among other things, the diffusivity. The ODE model does not include diffusivity, and so this most likely

explains the difference between the two models when the receptor cell is not included. Figures 4.11 and 4.12 show the PDE model's prediction of the amount in the skin and donor cell, respectively, over a three hour time interval. The permeability coefficient affects only the rate of absorption into the receptor, so it does not affect the prediction in the skin for the PDE model. The sum of squared deviations for the amount in the skin (using the mean of several sets of experimental data as the correct value) is 0.2867 and 0.0064 for the amount in the donor.

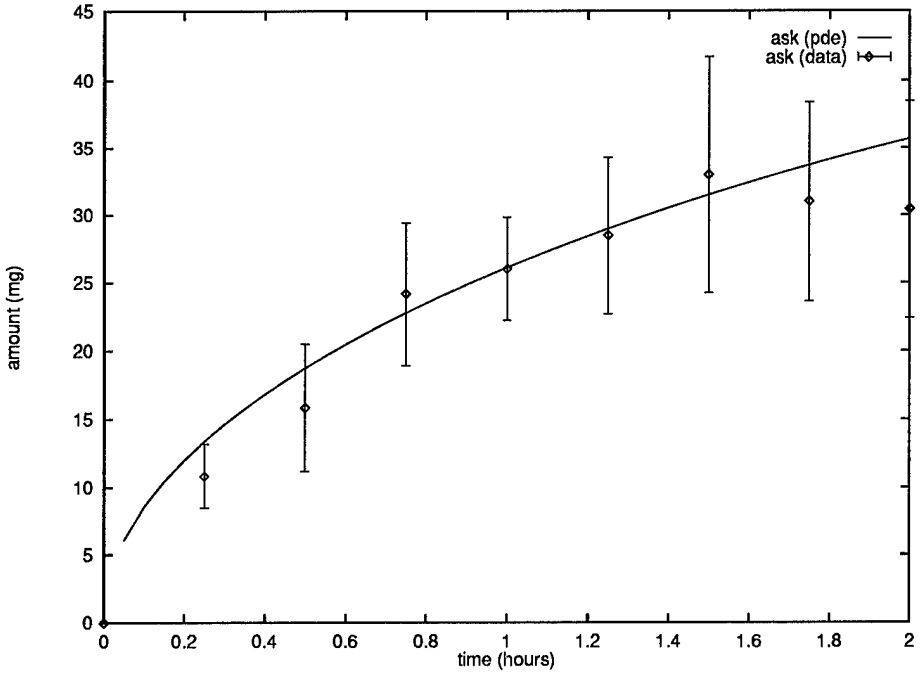

Figure 4.11 Aqueous Butyl Rubber PDE Model with No Receptor. The graph shows how well the PDE model matches the experimental data for the skin compartment.

4.3.4 Aqueous DBM Through Butyl Rubber With Receptor. The addition of the donor compartment in the model improves the prediction of the amount in the skin substantially. For exposure times less than one hour, the amount in the skin was high, but eventually leveled off into agreement with both the data and the ODE model. By adding the donor compartment, the amount of chemical going into the

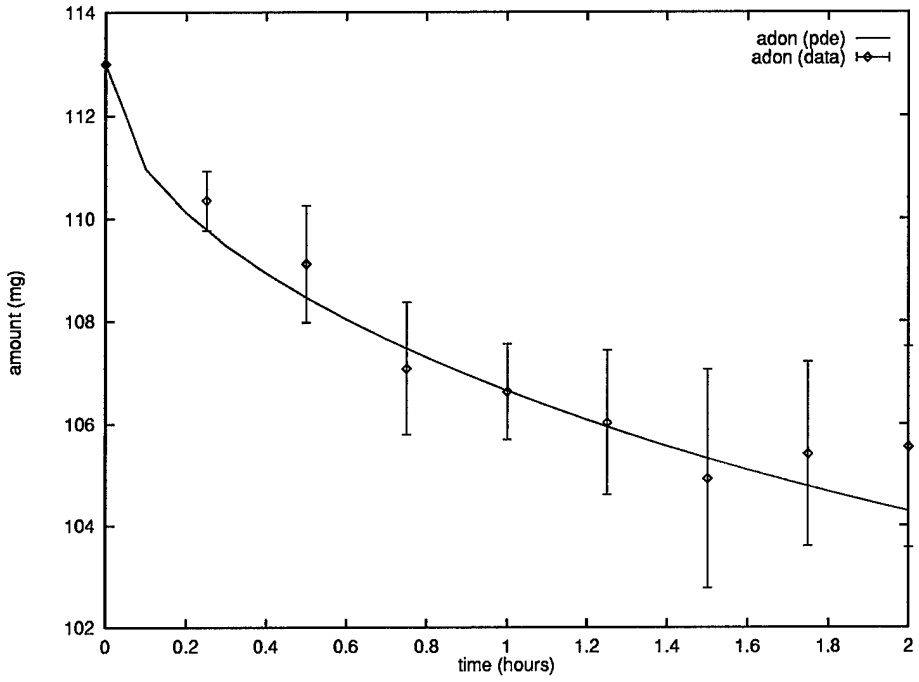

Figure 4.12 Aqueous Butyl Rubber PDE Model with No Receptor. The graph shows how well the PDE model matches the data for the donor cell.

skin does not increase quite as rapidly. Explicitly modeling the donor compartment makes sense physiologically as well, since the earlier model was based on a still earlier assumption by Cleek and Bunge that the amount at the interface between the donor and the rubber reaches equilibrium immediately [10]. The predictions for the amount in the skin for both the ODE and the PDE model are very close, not only to each other, but also to the laboratory data (Figures 4.13 and 4.6). The PDE model, however, more closely matches the data for the amount in the receptor. For the 120 hour prediction, the sum of squared deviations is 0.3258 for the amount in the rubber, 0.207 for the amount in the donor, and 0.0495 for the amount in the receptor.

4.3.5 Sensitivity Analysis for the PDE Model. Nearly all parameters used in both models were measured in the laboratory, and there is a good deal of confidence that those parameters' values are accurate. In the case of the ODE model,

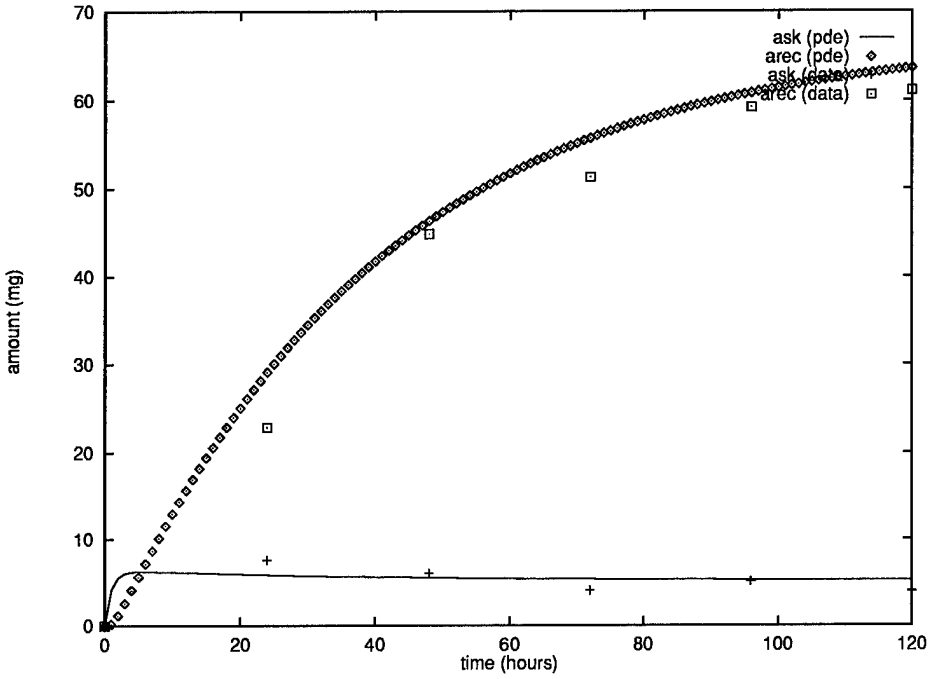

Figure 4.13 Aqueous Butyl Rubber PDE Model Results. The PDE model accurately predicts the amount in both the rubber and in the receptor. The permeability coefficient for this prediction is 0.22.

Model	Membrane	Donor	Skin	Receptor
ODE	Rat Skin	5.02×10^{-8}	0.0003	0.0029
ODE	Butyl Rubber No Receptor	0.0632	1.2274	
ODE	Butyl Rubber With Receptor	0.06760	0.3922	0.1274
PDE (modified)	Rat Skin	9.3244×10^{-6}	0.2177	0.1452
PDE (modified)	Butyl Rubber No Receptor	0.0064	0.2867	
PDE (modified)	Butyl Rubber With Receptor	0.0186172	0.3262	0.0438
PDE (original)	Rat Skin	0.0011	10.7914	21.8568

Table 4.1 Sum of Squared Deviations for the ODE and PDE Models

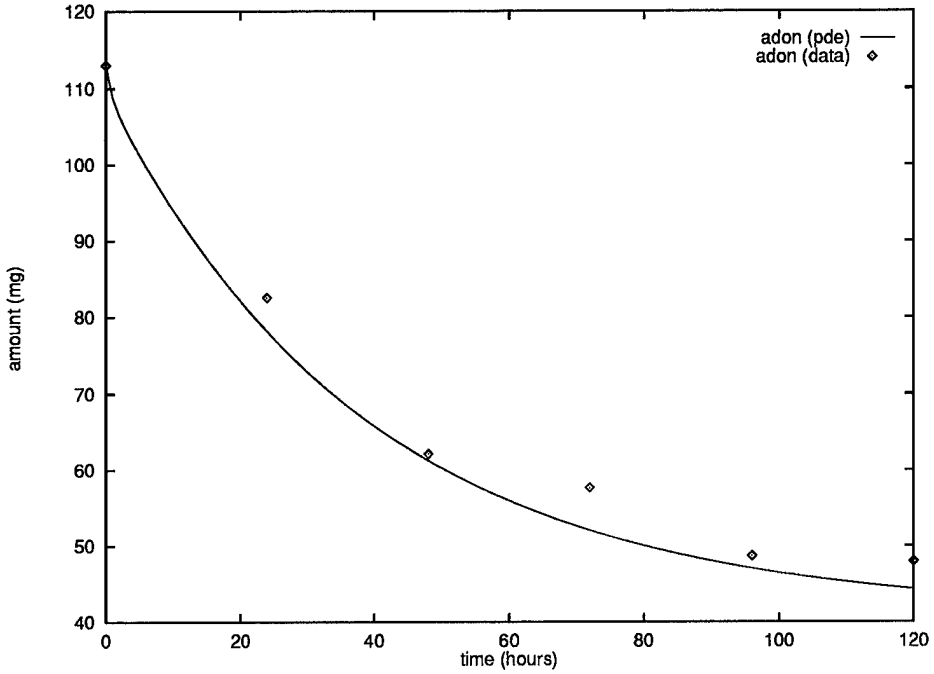

Figure 4.14 Aqueous Butyl Rubber PDE Model Results. The PDE model accurately predicts the amount in the donor compartment. The permeability coefficient for this prediction is 0.22.

the permeability coefficient, which is actually an average of the permeabilty between both interfaces of the rubber, is the only parameter not measured experimentally. For the PDE model, the permeability is between the skin (or rubber) and the receptor cell, and it also not determined experimentally. We performed a sensitivity analysis on the permeability to determine how much it affects the results of the model.

The PDE model's predictions are sensitive to the permeability. Changing the value by five percent in most cases results in a much larger effect on the total sum of squared deviations. However, a change in the permeability generally does not affect the predictions for all three compartments equally. Table 4.2 shows the sum of squared deviations for both models after the permeability coefficient is increased five percent.

Model	Membrane	Donor	Skin	Receptor
ODE	Rat Skin	1.915×10^{-6}	0.0083	0.1151
ODE	Butyl No Receptor	0.0639	1.2418	
ODE	Butyl With Receptor	0.0824	0.3940	0.1611
PDE (modified)	Rat Skin	6.7848×10^{-4}	0.2764	0.2965
PDE (modified)	Butyl No Receptor	0.0065	0.2867	
PDE (modified)	Butyl With Receptor	0.0207	0.3258	0.0495
PDE (original)	Rat Skin	0.0012	10.6105	34.3409

Table 4.2 The table shows the effect a five percent increase in the permeability has on the prediction.

4.4 Summary

There are three scenarios for which we examined the predictions of both the ODE and the PDE models. We have worked with a short term, two intermediate term, and one long term prediction. This was primarily because of limitations of the laboratory data available, but it does enable us to obtain a reasonable evaluation of the strengths and weaknesses of both models.

For short term aqueous DBM through rat skin, the ODE model clearly appears to provide a better match of the data. The deviations are very slight and the shapes of both curves are correct. The PDE model, however, also provides a reasonably accurate prediction, although the amount in the skin is slightly high.

Adapting the model to predict concentrations of neat DBM in all compartments is a subject of further study. Neither model adequately predicted the amount of chemical absorbed into the rubber, although by varying the initial concentration or permeability parameters the amount in the receptor at equilibrium could be reached.

For predictions of intermediate duration in cases without a receptor cell, intended to simulate absorption only into the skin, the PDE model provided better results. This is most likely because the model incorporates the diffusivity, rather than the permeability into the differential equation for the skin. The ODE model generally produced results that were considerably lower than expected in this case.

For long term aqueous DBM through rubber, both models' predictions were generally on target. Both closely matched the values for the rubber for the experimental data. The PDE model, however, more closely matched the amount in the receptor at each time interval. In addition, the shapes of both curves in the graph are nearly the same.

V. Summary and Conclusions

5.1 Summary

The goal of this research was to evaluate two previously developed PBPK models, an ordinary differential equation model and a partial differential equation model, then further develop the PDE model in order to improve its prediction of mammalian blood concentrations following exposure to aqueaous or neat liquid chemicals. The predictions of both models was compared to both experimental laboratory data and the predictions of earlier implementations of the models. This research resulted in a substantial improvement in the PDE model's predictions. Sensitivity analysis of the models' free parameter, the permeability coefficient, showed the effect that it has on the models' predictions.

5.2 Conclusions

Although both models treat the membrane as a single homogeneous compartment, they predicted the amounts in all compartments with reasonable accuracy. In some cases, the predictions at equilibrium were slightly better than those for short-term exposures, particularly for the PDE model. In general, the best model to use is the simplest one whose predictions are within a desired tolerance. Because the predictions of both models are roughly the same, and the ODE model is less complex, the ODE model may be the most appropriate for most applications. However, in cases where the amount of chemical at a certain point inside the membrane is needed, the PDE model is more advantageous, as its membrane model is more detailed.

Almost all of the parameters in both models have been measured experimentally. Because the permeability coefficient was estimated, we consider it to be a free parameter. Sensitivity analysis provided insight into how much its value affected the predictions of the models. The ODE model is much more dependent on permeability than the PDE model. However, the PDE model was impacted much more by changes

in the diffusivity and the lag time, parameters that can be measured empirically but not used in the ODE model. In any case, these are the most important parameters for these types of models.

There is tremendous potential for biologically-based mathematical models to provide species, dose, and duration extrapolations of laboratory experiments. Models such as these are both predictive and descriptive, and successfully extrapolating the experiments could have a substantial impact on pharmacology and toxicology. Accurately predicting membrane and receptor concentrations are dependent on developing models with a sound biological basis. Furthermore, the parameters in the models should be measurable in laboratory experiments on animals and humans. Both of the models in this thesis have the potential for extrapolation to humans once appropriate measurements of the parameters is performed.

5.3 Recommendations

Adapting these models to predict membrane and receptor concentrations after exposure to neat chemicals or vapor exposure would allow the models to handle different types of exposure. Applying both of the models in this research to other chemicals with different properties may possibly provide more insight into how substances with various chemical properties penetrate membranes.

Porting the PDE model with the improved boundary conditions to a PC platform using the LSODE libraries would take advantage of the computational power of desktop computers. Having the LSODE source code allows for the code to be ported to a variety of different platforms allowing greater flexibility than the proprietary IMSL library. Although the programs written to use IVPAG can successfully solve the system of equations in the PDE model, the LSODE program can not solve it yet.

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Vita

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13. ABSTRACT *(Maximum 200 words)*

Understanding the processes involved in dermal penetration of chemicals and drugs is important to both toxicologists and pharmacologists. Researchers developing new drugs are interested in enhancing the penetration of chemicals through the skin, while environmental professionals are interested in limiting such penetration. For both types of applications, predictive biologically-based mathematical models can be very useful in understanding the processes involved, particularly when such models are based on physiological and biochemical parameters which can be measured experimentally. In this thesis we study two existing physiologically-based pharmacokinetic (PBPK) models that predict concentrations of neat and aqueous dibromomethane (DBM) absorbed into and through different types of membranes, namely rat skin and butyl rubber. We evaluate the models and add modifications as necessary to improve the predictions. Nearly all of the parameters in these two models are measured experimentally in a laboratory. Sensitivity analysis on the permeability coefficient, the only parameter that is estimated, shows how much of an effect that parameter has on the models' predictions. The objective in studying and developing these models is to gain a better understanding of the absorption process by first modeling simple membranes such as butyl rubber, and extrapolating the results for rat skin to other species such as humans.

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